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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/461,090	12/14/1999	AXEL ULLRICH	2923-0347	3321

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EXAMINER
LU, FRANK WEI MIN

ART UNIT	PAPER NUMBER
1634	

DATE MAILED: 09/23/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Advisory Action	Application No.	Applicant(s)	
	09/461,090	ULLRICH ET AL.	
	Examiner	Art Unit	
	Frank W Lu	1634	

--The MAILING DATE of this communication appears on the cover sh t with th correspond nce address --

THE REPLY FILED 20 August 2003 FAILS TO PLACE THIS APPLICATION IN CONDITION FOR ALLOWANCE. Therefore, further action by the applicant is required to avoid abandonment of this application. A proper reply to a final rejection under 37 CFR 1.113 may only be either: (1) a timely filed amendment which places the application in condition for allowance; (2) a timely filed Notice of Appeal (with appeal fee); or (3) a timely filed Request for Continued Examination (RCE) in compliance with 37 CFR 1.114.

PERIOD FOR REPLY [check either a) or b)]

a) ☒ The period for reply expires 3 months from the mailing date of the final rejection.

b) ☐ The period for reply expires on: (1) the mailing date of this Advisory Action, or (2) the date set forth in the final rejection, whichever is later. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of the final rejection.
ONLY CHECK THIS BOX WHEN THE FIRST REPLY WAS FILED WITHIN TWO MONTHS OF THE FINAL REJECTION. See MPEP 706.07(f).

Extensions of time may be obtained under 37 CFR 1.136(a). The date on which the petition under 37 CFR 1.136(a) and the appropriate extension fee have been filed is the date for purposes of determining the period of extension and the corresponding amount of the fee. The appropriate extension fee under 37 CFR 1.17(a) is calculated from: (1) the expiration date of the shortened statutory period for reply originally set in the final Office action; or (2) as set forth in (b) above, if checked. Any reply received by the Office later than three months after the mailing date of the final rejection, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

1. ☐ A Notice of Appeal was filed on _____. Appellant's Brief must be filed within the period set forth in 37 CFR 1.192(a), or any extension thereof (37 CFR 1.191(d)), to avoid dismissal of the appeal.

2. ☒ The proposed amendment(s) will not be entered because:

   (a) ☒ they raise new issues that would require further consideration and/or search (see NOTE below);

   (b) ☒ they raise the issue of new matter (see Note below);

   (c) ☐ they are not deemed to place the application in better form for appeal by materially reducing or simplifying the issues for appeal; and/or

   (d) ☐ they present additional claims without canceling a corresponding number of finally rejected claims.

   NOTE: _____.

3. ☐ Applicant's reply has overcome the following rejection(s): _____.

4. ☐ Newly proposed or amended claim(s) _____ would be allowable if submitted in a separate, timely filed amendment canceling the non-allowable claim(s).

5. ☐ The a)☐ affidavit, b)☐ exhibit, or c)☐ request for reconsideration has been considered but does NOT place the application in condition for allowance because: _____.

6. ☐ The affidavit or exhibit will NOT be considered because it is not directed SOLELY to issues which were newly raised by the Examiner in the final rejection.

7. ☒ For purposes of Appeal, the proposed amendment(s) a)☒ will not be entered or b)☐ will be entered and an explanation of how the new or amended claims would be rejected is provided below or appended.

   The status of the claim(s) is (or will be) as follows:

   Claim(s) allowed: _____.

   Claim(s) objected to: _____.

   Claim(s) rejected: 22-36.

   Claim(s) withdrawn from consideration: _____.

8. ☐ The proposed drawing correction filed on _____ is a)☐ approved or b)☐ disapproved by the Examiner.

9. ☐ Note the attached Information Disclosure Statement(s)(PTO-1449) Paper No(s). _____.

10. ☐ Other: _____

DETAILED ACTION

ADVISORY ACTION

1. The proposed amendments filed on August 20, 2003 have been fully considered but will not be entered because: (1) they raise new issues that would require further consideration and/or search; and (2) they raise the issue of new matter.

The phrase "a G protein or G protein coupled receptor initiated extracellular signal pathway" in claim 22 raises the issue of new matter since the phrase "G protein initiated extracellular signal pathway" can not found in the specification and the examiner considers that protein coupled receptor initiated extracellular signal pathway is a correct phrase to be used in claim 22.

The phrase "further comprising a second cell which is different from the cell containing the receptor tyrosine kinase, wherein said compound affects said second cell." in claim 32 raises new issues that would require further consideration and/or search because this phrase is vague and indefinite in view of claims 22 and claim 32. The cell recited in claim 22 has a disturbed G-protein mediated signal transduction and a receptor tyrosine kinase capable of activation by G-protein mediated signal and the cell recited in claim 32 is different from the cell containing the receptor tyrosine kinase, it is unclear what is a difference between the cell recited in claim 22 and the cell recited in claim 32. Since the compound recited in claim 1 can affect the cell recited claim 22 and the cell recited in claim 32, it appears that the difference between the cell recited in claim 22 and the cell recited in claim 32 is not due to lack of the receptor tyrosine kinase in the cell recited in claim 32.

2. The examiner agrees to withdraw the objection on claim 27.

Response to Argument

In page 6, last paragraph bridging to page 11, last paragraph of applicant's remarks, applicant argues that (1) "[A]pplicants respectfully point out that at the time of the present invention, it was believed that the correlation between G protein activation and the activation of tyrosine phosphorylation of EGFR was mediated by an intracellular pathway. Thus, one skilled in the art would not have expected batimastat, which acts on an extracellular pathway of EGFR, to be capable of modulating a G protein mediated signal transduction. As stated on page 6 of the office action, Dong does not directly show that their method is related to modulation of G-protein mediated signal transduction. In addition, Dong does not indicate that the cells he used have a disturbed G-protein mediated signal transduction as required in the present claims. Applicants contend that in view of the knowledge in the art, one skilled in the art would not have been motivated to modify Dong's method to modulate G protein mediated signal transduction in a cell having a disturbed G-protein mediated signal transduction."; (2) "In addition, at the bottom of page 5, under point (2), the office action states: 'since it is known that reduction of tyrosine phosphorylation of a receptor is correlated to activation of G protein, batimastat used in the method of Dong et al. also modulate G protein mediated signal transduction.' Applicants point out that this statement is both incomplete and incorrect. A correlation of G protein activation and the activation of tyrosine phosphorylation of EGFR was indeed known in the art (e.g. Daub et al).

It was assumed, however, that this correlation is mediated by an intracellular pathway. Thus, prior to the present invention, one skilled in the art could not reasonably have expected that batimastat as used in the method of Dong et al. (which acts on an extracellular activation pathway of EGFR) would be capable of modulating a G protein mediated signal transduction. The activation of receptor tyrosine kinases such EGFR can be effected via a plurality of different pathways. As explained in detail below, a number of different stimuli were known, in addition to the activation of G proteins, which were correlated with EGFR tyrosine phosphorylation at the time of the Dong et al publication.".

These arguments have been fully considered but they are not persuasive toward the withdrawal of the rejection. First, applicant agrees with applicant that "one skilled in the art would not have expected batimastat, which acts on an extracellular pathway of EGFR, to be capable of modulating a G protein mediated signal transduction." However, since signal transduction mechanism of a cell is considered as an inherent property of the cell, metalloprotease-mediated ligand release taught by Dong *et al.,* is mediated by the extracellular domain of EGF receptor even through one having ordinary skill in the art at the time the invention was made may not consider that batimastat as used in the method of Dong *et al.,* modulates a G protein mediated signal transduction by acting on an extracellular EGFR but instead modulates a G protein mediated signal transduction by an *intracellular* mechanism. Second, there is no evidence to show that the cells used by Dong *et al.,* (HMEC line 184A1) does not have a disturbed G-protein mediated signal transduction as suggested by applicant. In fact, it is known that HMEC line has a G-protein mediated signal transduction. For example, see Tiruppathi et al.,

(PNAS, 97, pages 7440-7445, 2000). Third, although the examiner agrees with applicant that "a number of different stimuli were known, in addition to the activation of G proteins, which were correlated with EGFR tyrosine phosphorylation at the time of the Dong et al publication.", this is not a case here. Since the invention of this instant application and Dong *et al.,* use the same metalloprotease inhibitor, batimastat, to study the effect of EGFR on G-protein mediated signal transduction pathway, identical compound (ie., batimastat) must have an identical effect on the G-protein mediated signal transduction pathway and must follow the same mechanism. Furthermore, there is no evidence to show that metalloprotease-mediated ligand release taught by Dong *et al.,* is not mediated by the extracellular domain of EGF receptor.

3. Papers related to this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Group 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notices published in the Official Gazette, 1096 OG 30 (November 15, 1988), 1156 OG 61 (November 16, 1993), and 1157 OG 94 (December 28, 1993)(See 37 CAR § 1.6(d)). The CM Fax Center number is either (703) 308-4242 or (703)305-3014.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Frank Lu, Ph.D., whose telephone number is (703) 305-1270. The examiner can normally be reached on Monday-Friday from 9 A.M. to 5 P.M.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion, can be reached on (703) 308-1119.

Any inquiry of a general nature or relating to the status of this application should be directed to the patent Analyst of the Art Unit, Ms. Chantae Dessau, whose telephone number is (703) 605-1237.

Frank Lu
September 12, 2003

ETHAN WHISENANT
PRIMARY EXAMINER